



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> :  <b>A61K 31/38, 31/39, 31/40, 31/415, 31/42, 31/425, 31/44, 31/445, 31/495, 31/505, 31/095, 31/18, C07D 207/09, 233/54, 239/24, 241/04, 263/02, 277/28, 307/00, 333/00, 209/10, C07C 303/00, 307/00, 309/00, 311/00, 313/00</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 98/50029</b></p>
		<p>(43) International Publication Date: 12 November 1998 (12.11.98)</p>
<p>(21) International Application Number: <b>PCT/US98/09296</b></p>		
<p>(22) International Filing Date: <b>7 May 1998 (07.05.98)</b></p>		
<p>(30) Priority Data:  <b>08/852,858 7 May 1997 (07.05.97) US</b></p>		
<p>(71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; Office of Technology Transfer, 911 Williams Pitt Union, Pittsburgh, PA 15260 (US).</p> <p>(72) Inventors: SEBTI, Said, M.; 8957 Magnolia Chase Circle, Tampa, FL 33647 (US). HAMILTON, Andrew, D.; 1 White Pine Lane, Guilford, CT 06437 (US). AUGERI, David, J.; 6846 3rd Avenue, Kenosha, WI 53143 (US). BARR, Kenneth, J.; 4828 N. Hermitage #3A, Chicago, IL 60640-4143 (US). DONNER, Bernard, G.; 1901 McRae Lane, Mundelein, IL 60060 (US). FAKHOURY, Stephen, A.; 517 Buckingham, Mundelein, IL 60060 (US). JANOWICK, David, A.; 37070 Ganster Road, Beach Park, IL 60087 (US). KALVIN, Douglas, M.; 1201 Lockwood Drive, Buffalo Grove, IL 60089 (US). LARSEN, John, J.; 10542 Alteglid Street, Melrose Park, IL 60164 (US). LIU, Gang; 838 Alderly Lane, Gurnee, IL 60031 (US). O'CONNOR, Stephen, J.; 2103 Washington Avenue, Wilmette, IL 60091 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). SHEN, Wang; 6215 Formoor Lane, Gurnee, IL 60031 (US). SWENSON, Rolf, E.; 285 Penny Lane, Grayslake, IL 60030 (US). SORENSEN, Bryan, K.; 2620 North Lewis Avenue, Waukegan, IL 60087 (US). SULLIVAN, Gerard M.; 2214 North Sunrise Drive, Round lake Beach, Illinois 60073 (US). SZCZEPANKIEWICZ, Bruce G.; 33720 Royal Oake Lane, Apt. 209, Gages Lake, Illinois 60030 (US). TASKER, Andrew S.; 6251 Eagle Ridge Drive, Gurnee, Illinois 60031 (US). WASICK, James I.; 28440 Dorie Lane, Waterford, Wisconsin 53185 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, Illinois 60015 (US).</p> <p>(74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby &amp; Cushman, Intellectual Property Group of Pillsbury Madison &amp; Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b>  <i>With international search report.</i>  <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>		

## (54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

## (57) Abstract

Compounds having formula (1) or a pharmaceutically acceptable salt thereof wherein R<sub>1</sub> is (a) hydrogen, (b) lower alkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl -L<sub>2</sub>-, and (i) heterocyclic -L<sub>2</sub>-; R<sub>2</sub> is selected from (a) formula (1), (b) -C(O)NH-CH(R<sub>14</sub>)-C(O)OR<sub>15</sub>, (c) formula (2), (d) -C(O)NH-CH(R<sub>14</sub>)-C(O)NH-SO<sub>2</sub>R<sub>16</sub>, (e) -C(O)NH-CH(R<sub>14</sub>)-tetrazolyl, (f) -C(O)NH-heterocyclic, and (g) -C(O)NH-CH(R<sub>14</sub>)-C(O)NR<sub>17</sub>R<sub>18</sub>; R<sub>3</sub> is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, formula (3), and -P(W)R<sup>R3</sup>R<sup>R3'</sup>; R<sub>4</sub> is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L<sub>1</sub> is absent or is selected from (a) -L<sub>4</sub>-N(R<sub>5</sub>)-L<sub>5</sub>-, (b) -L<sub>4</sub>-O-L<sub>5</sub>-, (c) -L<sub>4</sub>-S(O)<sub>n</sub>-L<sub>5</sub>-, (d) -L<sub>4</sub>-L<sub>6</sub>-C(W)-N(R<sub>5</sub>)-L<sub>5</sub>-, (e) -L<sub>4</sub>-L<sub>6</sub>-S(O)<sub>m</sub>-N(R<sub>5</sub>)-L<sub>5</sub>-, (f) -L<sub>4</sub>-N(R<sub>5</sub>)-C(W)-L<sub>7</sub>-L<sub>5</sub>-, (g) -L<sub>4</sub>-N(R<sub>5</sub>)-S(O)<sub>p</sub>-L<sub>7</sub>-L<sub>5</sub>-, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) formula (4), and (m) formula (5) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.

